Tuberculosis

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Your commander calls you to discuss the issue of TB among Iraqi detainees held in your short term holding facility and what measures are in place to protect U.S. personnel.

12.26.2003 05:11

Clinical Scenario

- You receive a call reporting an Azerbaijani soldiers with active TB disease at a near by base in Iraq
- Someone decided to screen the other Azerbaijani soldiers revealing many with +PPD
  - They all received the BCG
  - None are symptomatic

Clinical Scenario

From: XXXXX.XXXXXX@us.army.mil
Sent: Monday, January 17, 2005 5:02 AM
To: id.consult@us.army.mil
Subject: TB med

Dear Sir

I am the flight surgeon for XXXXX and an ER Doc by training.

I have a soldier that I inherited from XXXXX.

Initially started on Dec 03 with positive PPD (only 4 mm), neg history, neg physical, neg sputum and negative CXR. He was not started on medicaition since it was just prior to deployment but told to start meds after reployment due to unavailability of lab. However upon deployment to LSA Anaconda, Iraq he found adequate lab service and was started on Isoniazid and B6. He has taken the medication for 6 months. His liver function test has been monitored with initial AST/ALT was 21/23 and in Sep 04 56/88 and currently is 87/151.

He continues to be healthy with no TB sx.

Clinical Scenario

Can I stop the medication? He was initially told to take med for 9 months by general practioner.

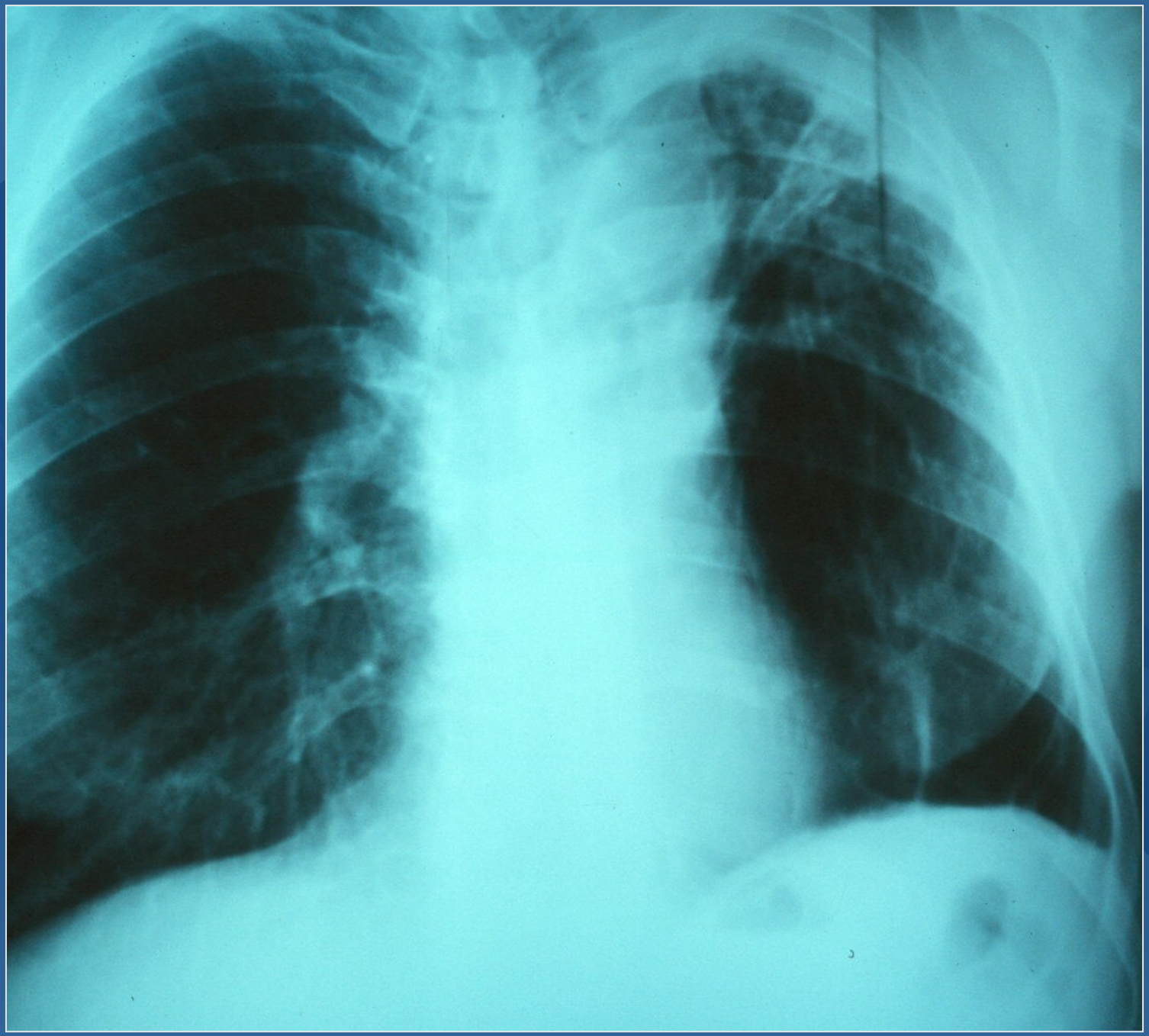
What are your recommendations for followup?

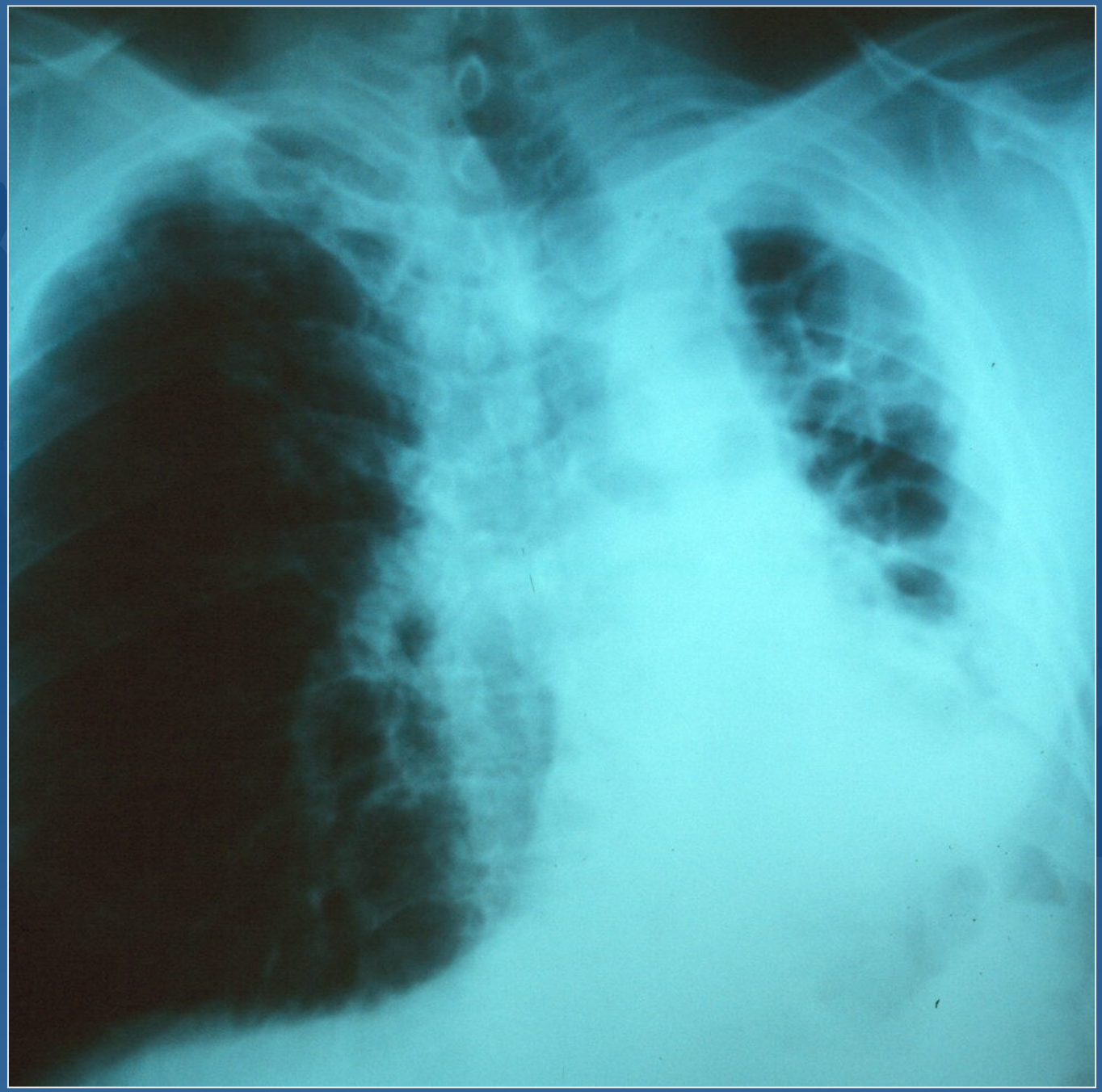
What are the paramenters to stop medication based on liver functions tests?

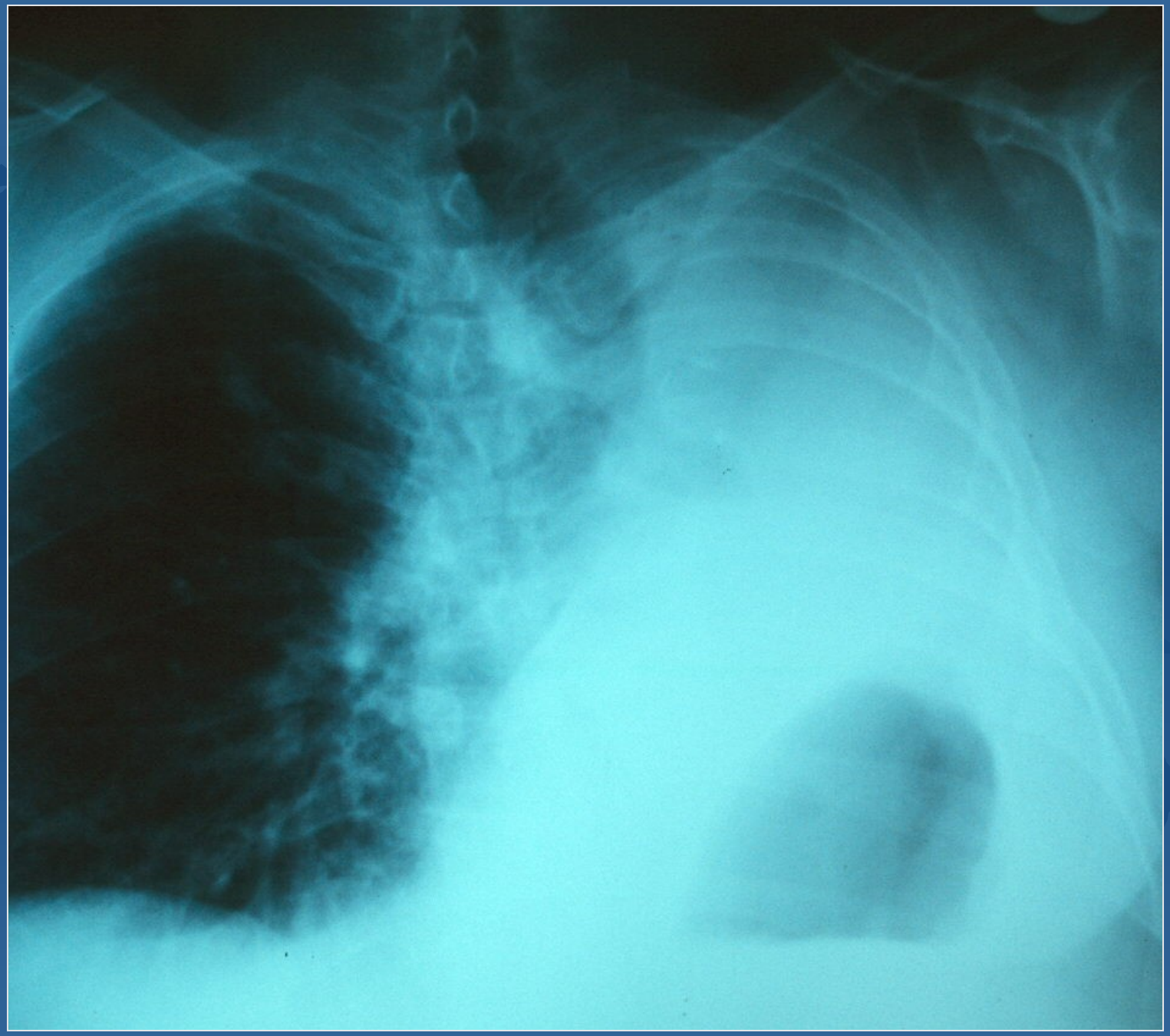
Please advise

Thanks,

XXXXXXX



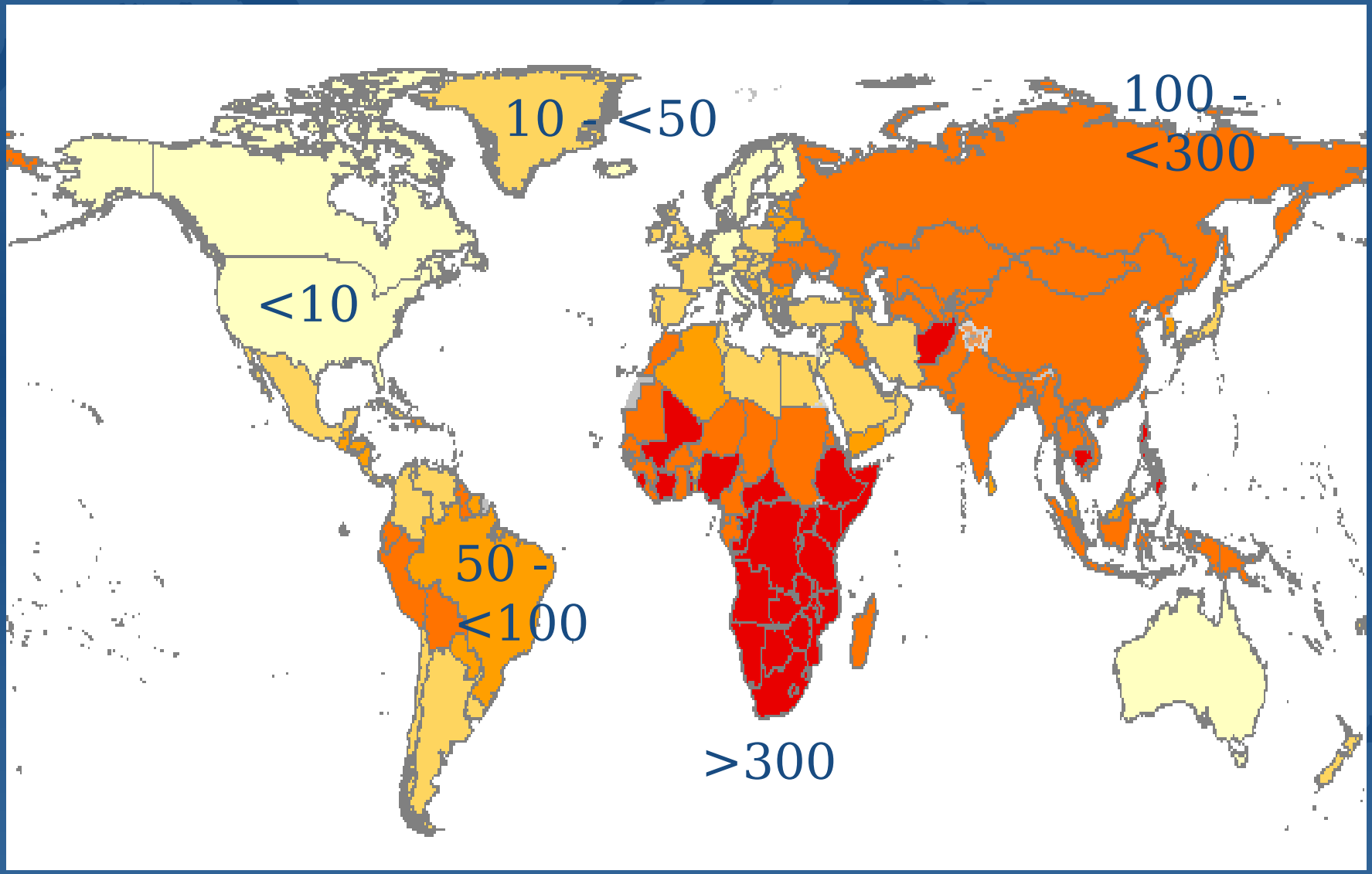




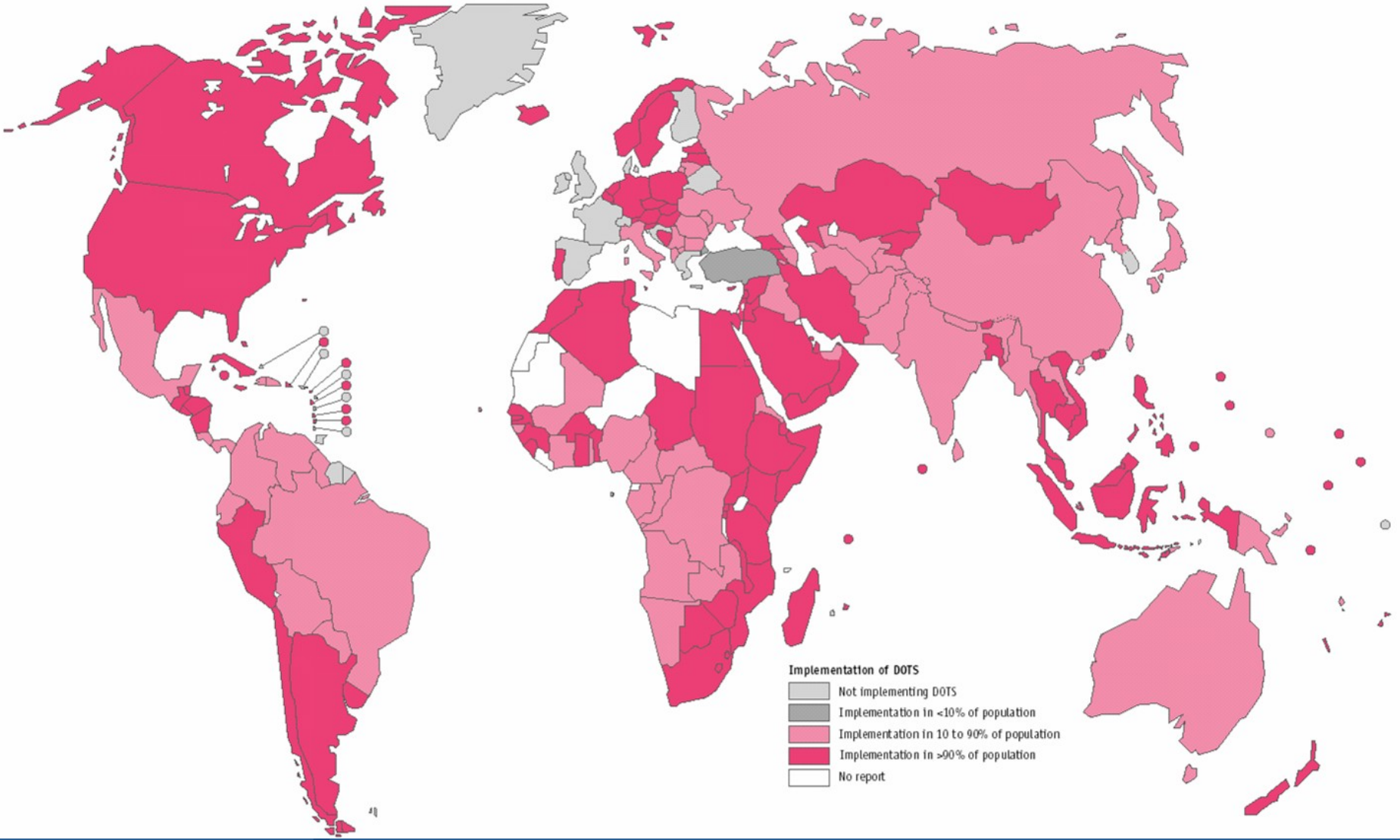
- Does the disease exist where we are?
- How do we contract the disease?
- How can we prevent transmission?
- What management strategies of LTBI and TB disease should we undertake?

Does the disease exist where we are?

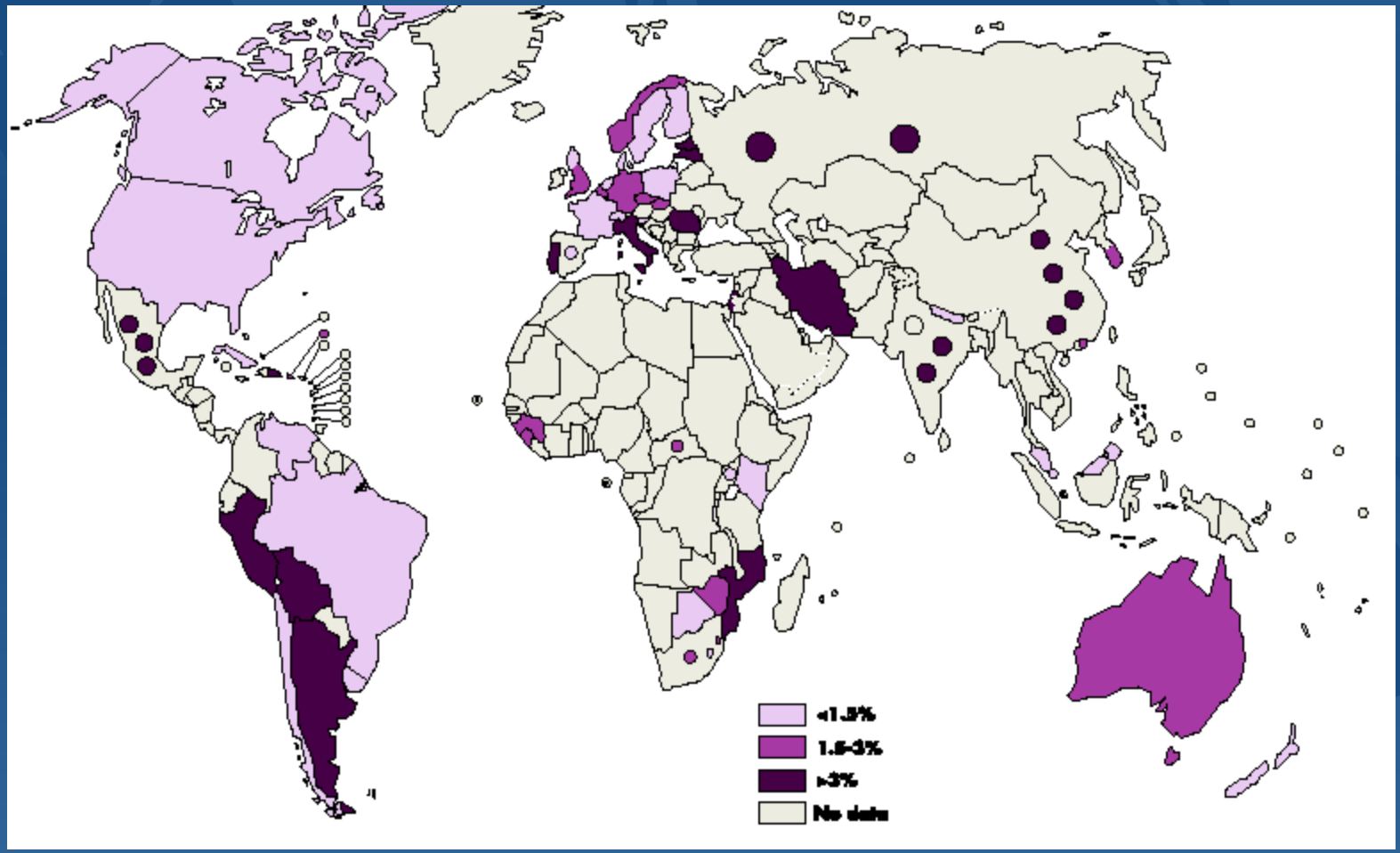
2004 TB Incidence (per 100,000)



3. Implementation of DOTS, 2002



Prevalence of MDR-TB, ‘94-’99



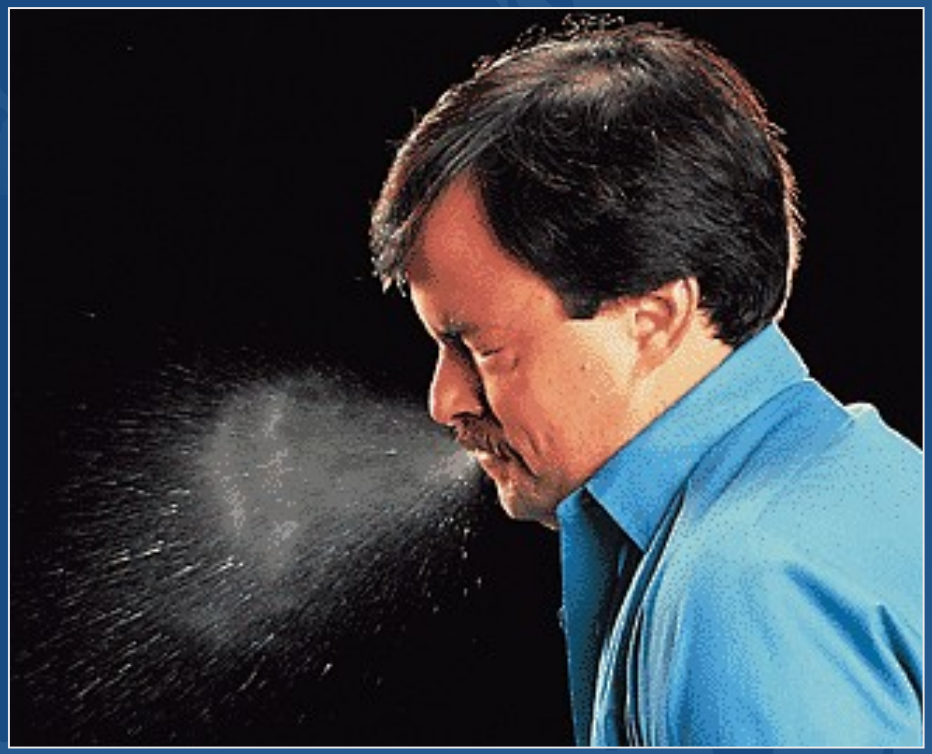
How do we contract the disease?

Transmission

- Close contacts at highest risk of becoming infected
  - Prolonged, frequent or intense exposure
  - Infection rate ~22% (similar if drug-resistant TB- but infectious longer)
- Person-to-person spread with active TB disease (not latent TB infection)

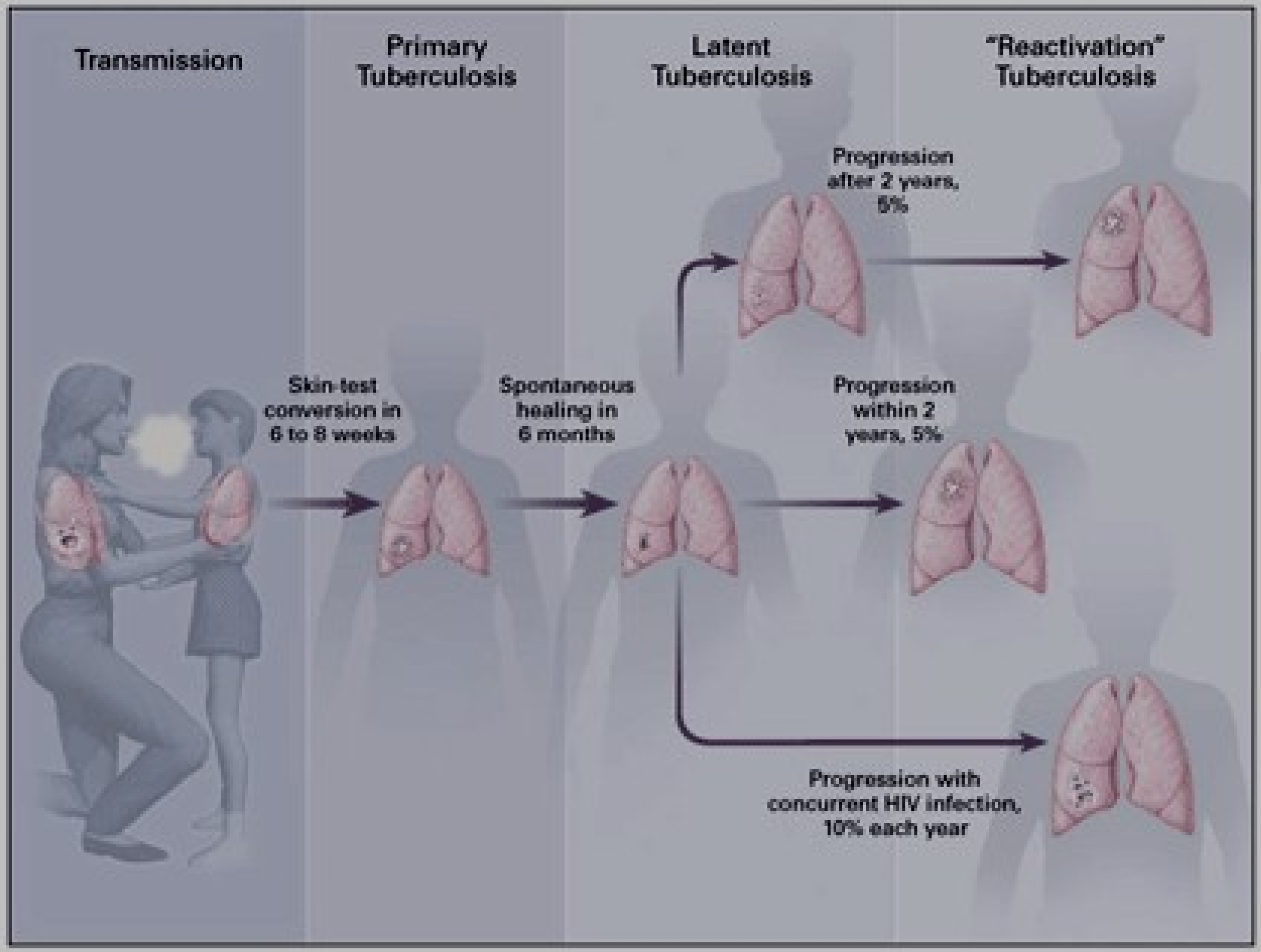
Transmission

- Spread by droplet nuclei (1-5 micron)
- Expelled
  - Coughing (3000 infectious droplet nuclei- measured at 200-300 mph up to 600 mph)
  - Speaking (5 min = 3000 droplet nuclei)
  - Singing
  - Sneezing



Probability of TB Transmission

- Infectiousness of person with TB
- Exposure
  - Environment
  - Duration
- Virulence of the organism
  - ? Noninfectious after 2 weeks of therapy (NY cavitary disease still smear + after 3 weeks of therapy
- Extrapulmonary is rarely contagious- except
  - Laryngeal TB
  - Aerosol-producing procedures- autopsies, tissue


Transmission
Primary Tuberculosis
Latent Tuberculosis
"Reactivation" Tuberculosis
Progression after 2 years, 5%
Skin-test conversion in 6 to 8 weeks
Spontaneous healing in 6 months
Progression within 2 years, 5%
Progression with concurrent HIV infection, 10% each year

Pathogenesis- Developing Disease

- In the US, 10% infected with TB develop disease
  - 5% infected with TB develop disease in first 1-2 years after infection
  - Another 5% will develop disease sometime in there lifetime
    - + PPD and nl CXR 0.03%/year
    - + PPD and abnormal CXR 1%/year

How can we prevent transmission?

- Screen sources
- Screen exposed
- Infection control practices

Must Rule-Out TB Disease

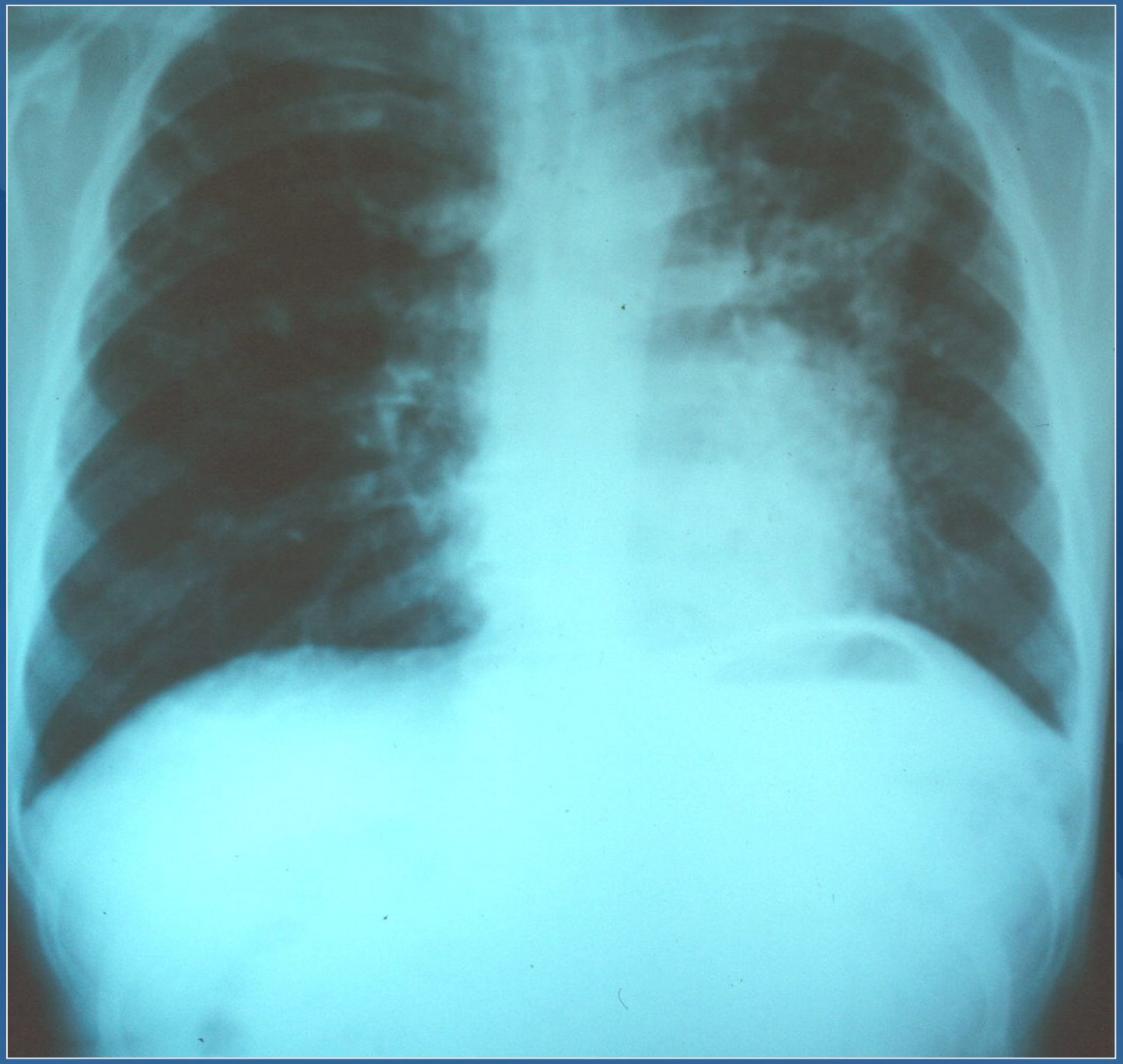
- Exposure, demographics, risks for HIV, h/o TB treatment, other illnesses that increase risk of TB disease
- Consider exposure to MDR-TB

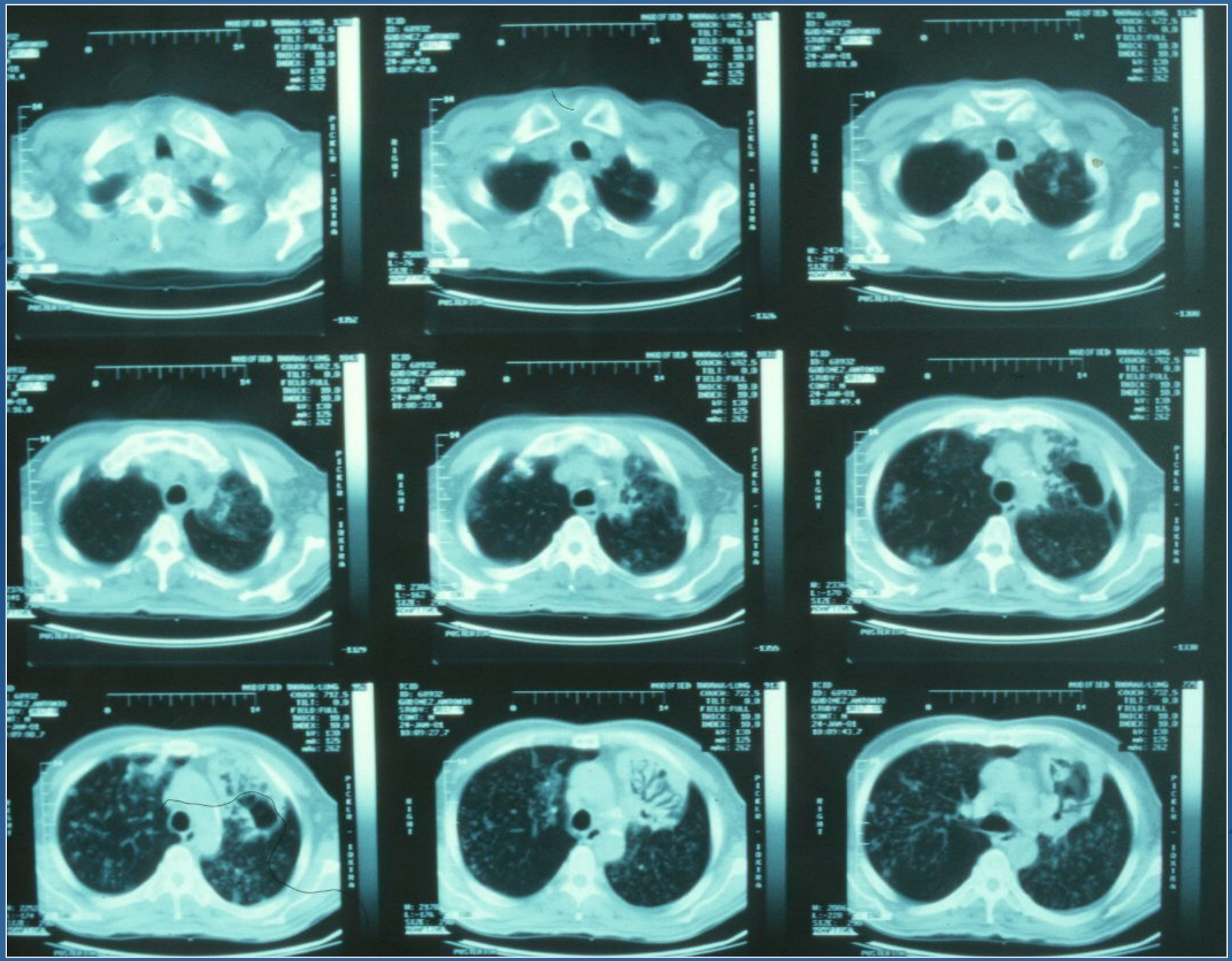
R/O TB Disease

- Productive cough, prolonged (≥ 3 weeks) cough, chest pain, and hemoptysis
- Systemic symptoms- fever, chills, night sweats, appetite loss, weight loss and easy fatigability
- 19% case are exclusively extrapulmonary
  - Back pain- TB spine
  - Hematuria- TB kidney

Diagnosis of TB

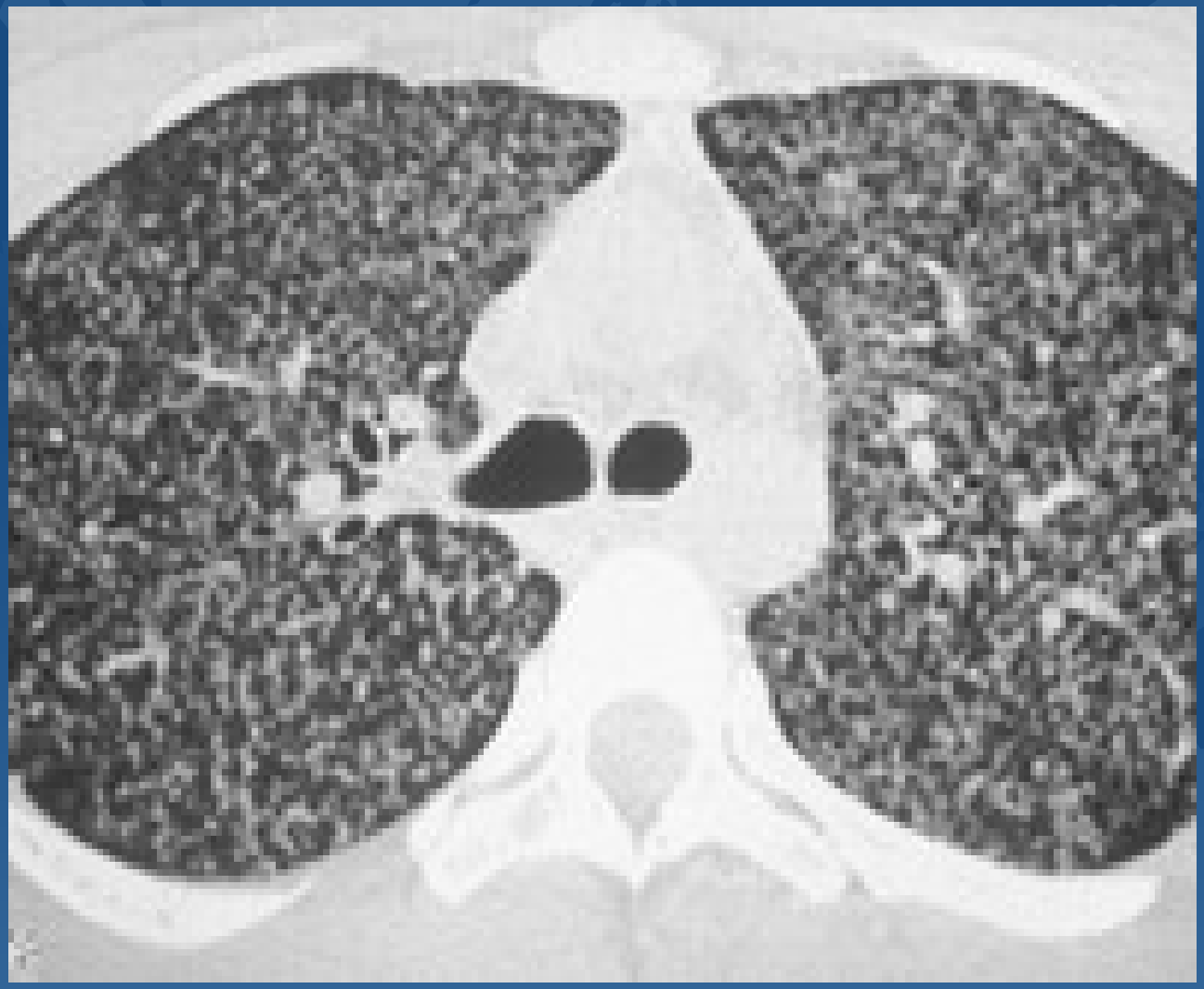
- Pulmonary TB
  - Primary TB pneumonia
    - Lobar consolidation, cavitary disease with middle or lower zone infiltrations, hilar adenopathy and atelectasis
    - Sputum highly positive
  - Postprimary (reactivation) TB
    - Upper lobe disease that often includes cavitation
    - Communicability is high





Miliary Disease

Miliary Disease

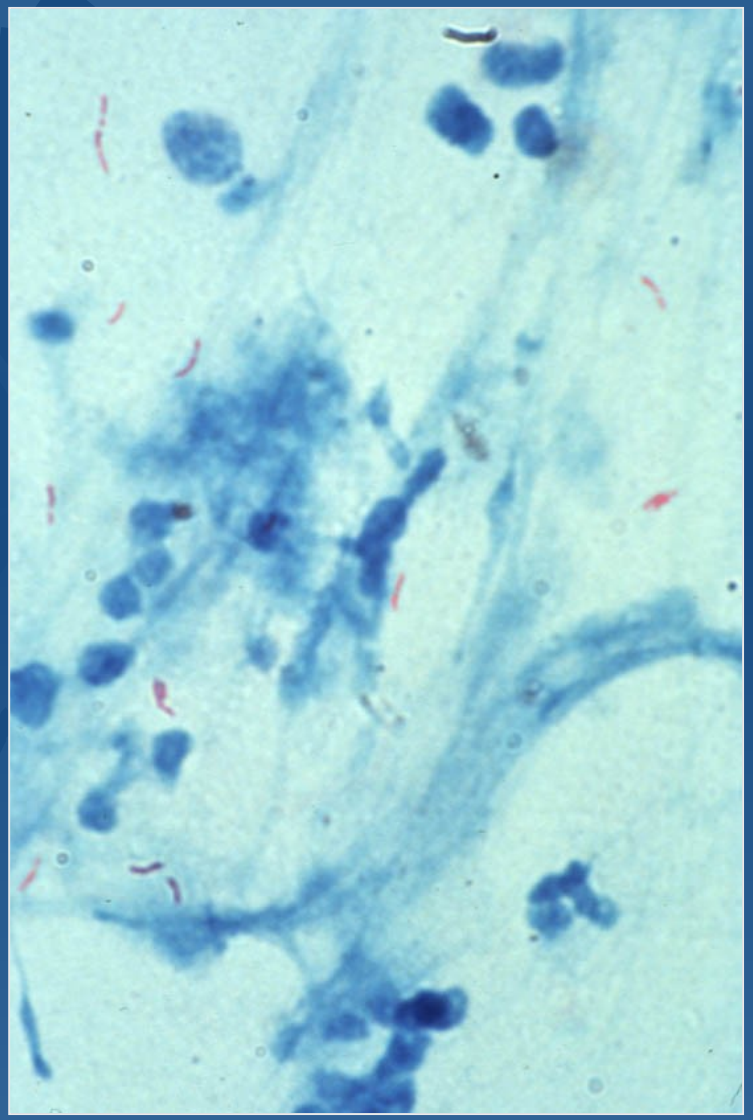


Diagnosis of TB- Microbiology

- Specimen collection - pulmonary and laryngeal
  - Obtain 3 sputum specimens for smear examination and smear culture- early morning
  - Persons unable to cough up sputum, induce sputum, bronchoscopy or gastric aspirate (highest yield may be AM sputum post bronchoscopy)
  - Follow infection control policy

Diagnosis of TB- Microbiology

- Fluorochrome staining with auramine-rhodamine is preferred [faster than Ziehl-Neelsen or Kinyoun (basic fuchsin dye)]
  - Presumptive diagnosis
  - 10,000 organisms/ml of sputum required for + stain
  - 10-100 viable organisms to have positive culture



Diagnosis of TB- Nucleic Acids

- Detects 10 organisms in clinical isolates
- Gene probe
  - Smear positive cases- sens/spec exceed 95%
  - Smear negative cases- sens 40-70%
- Other body fluids
  - Not FDA approved

Screen for LTBI

Preferred Testing Method

- Mantoux tuberculin skin test
- Occasionally more appropriate to test with CXR and sputum smear
  - Identify person who have current pulmonary TB and when treatment for LTBI is not the primary goal
    - High-turnover jails
    - Homeless shelters
    - Detainees

Tuberculin Skin Testing

- Inject ID 0.1 ml of 5 TU PPD tuberculin (SQ/leak)
- Wheal 6-10 mm in diameter
- Read reaction at 48-72 hours

Tuberculin Skin Testing

- Measure only induration- mm
  - Read perpendicular to the long axis of the forearm
  - Positive test- read up to 1wk
  - Repeat and reread if negative and not read in 72h
  - Some Vietnamese results not positive until 5-7 days
- Up to 25% with active pulmonary disease negative

Classification of Tuberculin Reaction

- Converter
  - IF tested in last 2 years and not meet criteria for LTBI
  - AND new PPD $\geq$ 10 mm change in size
  - THEN considered positive

Classification of Tuberculin Reaction

- ≥ 5 mm
  - HIV-positive person
  - Recent contacts of TB case
  - Persons with fibrotic changes on CXR c/w old healed TB
  - Patients with organ transplants and other immunosuppressed patients (receiving equivalent of ≥15 mg/day of prednisone for 2-4 weeks)

Classification of Tuberculin Reaction

- ≥ 10 mm
  - Recent arrivals (< 5 years) from high-prevalence area
  - Injection drug users
  - Residents and employees of high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health-care facilities, residential facilities for AIDS patients and homeless shelters

Classification of Tuberculin Reaction

- ≥ 10 mm
  - Mycobacteriology laboratory personnel
  - Persons with clinical conditions that place them at high risk
  - Children < 4 years of age, or children and adolescents exposed to adults in high-risk categories

Classification of Tuberculin Reaction

- ≥ 15 mm
  - All others- however, targeted skin testing programs should only be conducted among high-risk groups
  - Occasionally health care setting with low risk exposure

Inaccurate Results of PPD

Type of Reaction	Possible Cause
False-positive	Nontuberculous mycobacterium BCG vaccination
False-negative	Anergy Recent TB infection Very young age (< 6 months) Live-virus vaccination Overwhelming TB disease

ACIP- PPD done on same day or 4-6 weeks after live-virus measles vaccine

What About BCG Vaccinations?

- Effect of BCG on PPD was less then 15 yrs
- Positive skin test >15 mm unlikely to be due to BCG

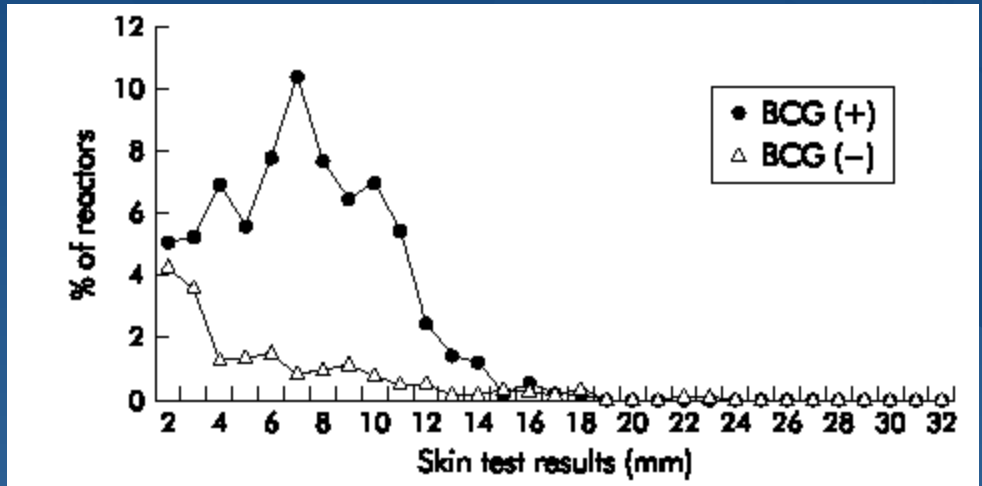


Figure 3 Percentage reactors versus skin test results in mm with 5 TU PPD (576 BCG+, 1145 BCG–).

Thorax

Alternative Diagnostic Strategies

- Quanti-FERON®TB
- Blood lab test

Infection Control

Consider infectious

- Coughing
- Undergoing cough-inducing or aerosol-generating procedures
- Have sputum smears positive for AFB and they
  - Are not receiving therapy
  - Have just completed therapy or
  - Have poor clinical response to therapy

Infection Control

No longer infectious if meet ALL of (? remove from isolation):

- Are on adequate therapy
- Have had a significant clinical response to therapy AND
- Have had 3 consecutive negative sputum smear results (not the same as 3 negative cultures- still small risk)

Infection Control

- Initially smear examinations every 1-2 weeks
- If not respond clinically to therapy in 2-3 weeks concern about adherence
- If drug-resistant TB infectiousness may last several weeks or months

Field Approach

- Possible source wears surgical mask
- Exposed personnel N-95 mask
- Examination in daylight
- Well ventilated area

BCG Vaccination

- Prevents serious forms of TB in children (?>80%)
- May cause + PPD, interfering with surveillance
- Do not use as part of assessment of results of tuberculin skin test reaction

BCG Recommended Vaccination

- HCW
  - High percentage of MDR-TB
  - Likely transmission of MDR-TB
  - Comprehensive TB infection-control precautions have been implemented and have not been successful

Management

- Active disease
- LTBI

Who Gets Treated?

- Determined by
  - Epidemiologic information
  - Clinical and radiographic features of the patient
  - Results of the initial series of AFB smears
  - Culture of mycobacteria

Treatment of TB Disease

- Before effective drugs
  - 50% died within 2 years of active pulmonary TB
  - 25% cured

Treatment of TB Disease

- Why so many drugs?
  - INH resistance 10^6 bacilli
  - SM resistance 10^6 bacilli
  - RIF resistance 10^8 bacilli
  - EMB resistance 10^5 bacilli
  - $1/10^6+10^6+10^8 = 1/10^{20}$
  - $10^{7\text{-}9}$ bacilli in a cavitary lesion ($10^{2\text{-}4}$ bacilli in fibrotic changes)

Treatment of TB Disease

- 4 drugs in areas with 4% primary resistance to INH in the community
- Focus on adherence
- Never add single agent to failing regimen
- Case management
- DOT

TB Disease Treatment Regimens

- Include 4 drugs in initial regimen
  - INH
  - RIF
  - PZA (allows 6 instead of 9 month regimen)
  - EMB >> SM (4th drug in cases of resistance)- can stop when susceptibilities return

TB Disease Treatment Regimens

- Initial phase 2 months (RIPE)
- Continuation phase (RI)
  - 4 months typically
  - 7 months
    - Cavitary pulmonary tb caused by drug-susceptible organisms whose sputum culture obtained at completion of 2 months of tx is +
    - Initial phase not include PZA
    - Treated once weekly INH and rifapentine whose sputum culture obtained at completion of initial phase is positive

Drug- Resistant TB

- TB resistant to INH treated 9-12 months (RIF, PZA, EMB or SM)
- MDR (INH and RIF resistance)- treated until culture converted to negative + 12 additional months (typically 18-24 months total duration)

Monitoring

- Baseline LAE, BUN/CR, CBC, uric acid (PZA), baseline visual acuity (EMB) and audiometry (SM)
- Minimum monthly monitoring with clinical assessment of adverse reactions
  - Stop immediately if n/v, loss of appetite, persistently dark urine, yellowish skin, malaise, elevated temp > 3 days, abdominal tenderness
  - Check labs if clinically indicated

Monitoring Response to Therapy

- Culture monthly until negative (X2 months)
  - 20% failure- have both cavitations on CXR and positive culture at 2 months
  - 5-6% failure- if 1 of the above
  - 2% failure- neither
- If MDR-TB monitor cultures monthly throughout entire treatment course
- CXR at completion of therapy

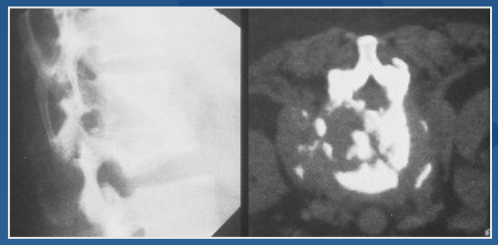
Monitoring Response to Therapy

- After 2-3 months of therapy, if cultures are positive or symptoms do not resolve, reevaluate for
  - Drug resistance
  - Malabsorption of drug
  - Laboratory error
  - Extensive disease
  - Adherence
- If cultures not negative at 2-3 months- ? DOT

Disease

- 73% affect the lungs exclusively
- Extrapulmonary sites
  - Pleural effusion
  - CNS
  - Lymphatic system
  - Genitourinary system
  - Bones and joints
  - Disseminated (miliary TB)
  - Less likely- breast, skin, peritoneum

- Extrapulmonary more common in immunosuppressed and young children
  - Especially lymphatic and disseminated



Treatment

- LTBI
  - Monitoring
  - Toxicity

Treatment of LTBI

- Candidates based upon PPD size and risks

Treatment of LTBI

- Close contacts- early negative PPD, with repeat test done at 10-12 weeks to confirm negative (then treatment d/c)
  - Children under 4 years of age
  - Immunosuppressed
  - Patients who may develop TB quickly after exposure

Treatment of LTBI

- Obtain sputum if symptoms or CXR c/w prior or healed TB OR HIV even without symptoms and normal CXR

LTBI Treatment Regimens

- 9-month INH regimen is optimal
  - 270 tabs/12months
  - Best option HIV+, and children HIV-
  - 2 X weekly DOT

Table 4. Efficacy of various durations of isoniazid preventive therapy for persons with fibrotic lesions, by length of treatment—International Union Against Tuberculosis (IUAT) Trial, 1969–1977

Group	5-yr Tuberculosis incidence* (% reduction)			
	Placebo	12 wk	24 wk	52 wk
All participants (n = 27,830)†	14.3	11.3 (21)	5.0 (65)	3.6 (75)
Adherent participants‡ (n = 21,635)§	15	9.4 (31)	4.7 (69)	1.1 (93)
Fibrotic lesions <2 cm^2 (n = 18,663)†	11.6	9.2 (20)	4.0 (66)	4.2 (64)¶
Fibrotic lesions >2 cm^2 (n = 8,428)§	21.3	16.2 (24)	7.0 (67)	2.4 (89)

* Per 1000 person-years.

† Comparing placebo to 24 and 52 wk, $p < 0.05$; differences between placebo and 12 wk and between 24 and 52 wk not significant.

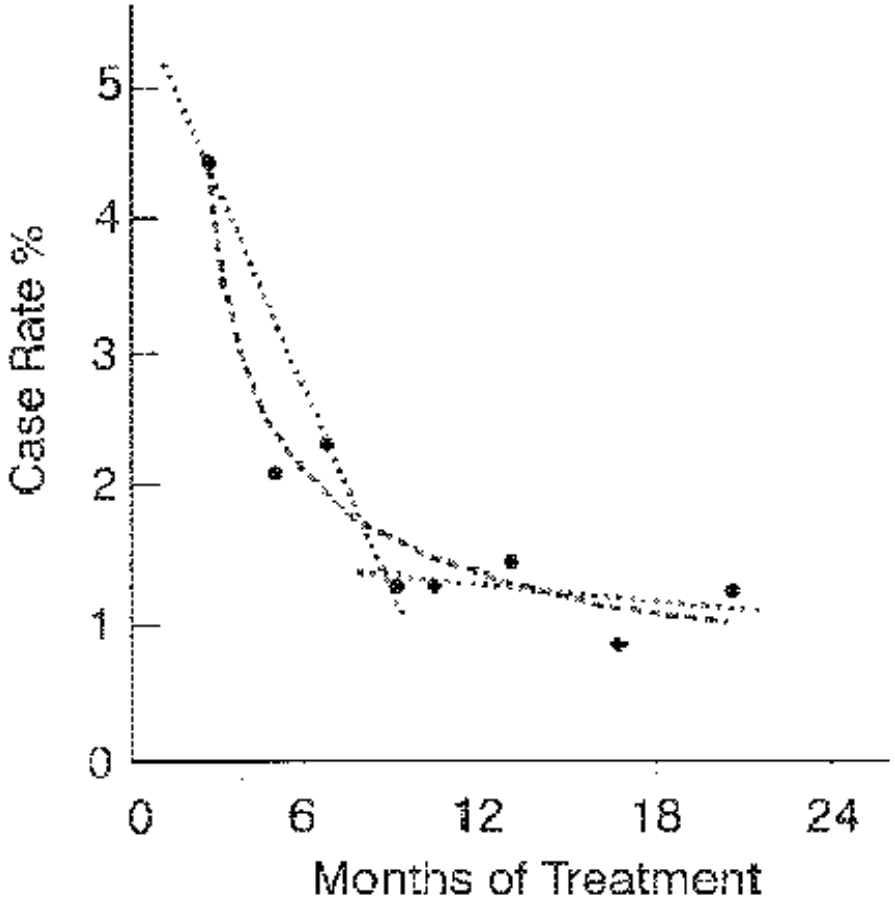
‡ Collected pill calendars for "almost all" of the months assigned for their regimen and had taken at least 80% of the pills from the calendar by the time of the next monthly visit.

§ For all interregimen comparisons ($p < 0.05$).

¶ Persons who developed tuberculosis on 52-wk regimen and had small fibrotic lesions were less likely to have collected pill calendars (47%) than all other groups (≥80%) ($p < 0.001$).

Source: International Union Against Tuberculosis Committee on Prophylaxis. Efficacy of vaious durations of isoniazid thereapy for tuberculosis: five years of follow-up in the IUAT trial. *Bull. WHO* 1982;60:555-64.

Figure 1*



*Tuberculosis case rates (%) in the Bethel Isoniazid Studies population according to the number of months isoniazid was taken in the combined programs. Dots represent observed values; thin line, the calculated curve (y=a+b/x); and dotted lines the calculated values based on the first four and the last five observations (y=a+bx). Source: Comstock, G.W. 1999. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? Int. J. Tuberc. Lung Dis. 3:847–850. Reprinted by permission of the International Union Against Tuberculosis and Lung Disease.

LTBI Treatment Regimens

- 6 months INH
- RIF/PZA
- Rifampin
  - 4 months (*in vitro*- limited human data: prospective randomized trial of TB + persons with silicosis and nonrandomized trial of persons exposed to INH resistant TB)

Monitoring

- Baseline LAE not needed unless H&P suggest liver disease
  - Baseline LAE indicated if HIV+, pregnant or 3 months postpartum, h/o chronic liver disease (hep B, C, ETOH)
- Routine monitoring LAE only if abnormal baseline and risk for hepatic disease

Monitoring

- Once a month f/u to assess adherence, s/s of active TB disease, s/s hepatitis
  - 10-20% mild, asymptomatic elevation of LAE with resolution
    - 3-5 ULN and monitor for side effects
  - RIF/PZA- 0, 2, 4, 8 week LAE

Monitoring

- Toxicity INH
  - Hepatotoxicity
    - Related to life long liver insult probably not age
    - Elevated AST/ALT, when elevated return to normal quickly (1-2 days) after stopping
  - Neuropathy: treat with vitamin B6- DM, uremia, alcoholism, malnutrition, HIV-infection, pregnant, h/o seizure disorder

What About Alcohol?

- Daily alcohol drinking- 26.5/1000 persons have abnormal LAE
- However, current recommendations are vague
  - Discourage binge drinking
  - Avoid large amounts of alcohol
  - Avoid multiple hepatotoxic agents (such as acetaminophen)

Clinical Scenario

- You receive a call reporting an Azerbaijani soldiers with active TB disease at a near by base in Iraq
- Someone decided to screen the other Azerbaijani soldiers revealing many with +PPD
  - They all received the BCG
  - None are symptomatic

Clinical Scenario

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What are your recommendations for followup?

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Please advise

THanks

Your commander calls you to discuss the issue of TB among Iraqi detainees held in your short term holding facility and what measures are in place to protect U.S. personnel.

- Screening
  - Detainees- clinical evaluation followed by CXR if necessary
  - U.S. personnel- pre and post deployment PPD
- Transmission avoidance
  - Outside evaluations or in UV light
  - Surgical mask on source
  - N-95 mask *if available*

Overview

- Does the disease exist where we are?
- How do we contract the disease?
- How can we prevent transmission?
- What management strategies of LTBI and disease should we undertake?

References

- Internet sites have most recent data
  - www.cdc.gov
  - www.who.int
- Treatment is often guideline based
  - www.idsociety.org

Questions?